

#54

The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper ~~195~~

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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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ROBERT C. ROSE, WILLIAM BONNEZ  
and RICHARD C. REICHMAN,

Junior Party,  
(Application 08/207,309)

v.

Senior parties:

DOUGLAS R. LOWY, JOHN T. SCHILLER  
and REINHARD KIRNBAUER,  
(Application 08/484,181)

Patent Interference 104,771

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C. RICHARD SCHLEGEL and A. BENNETT JENSON,  
(Application 08/216,506)

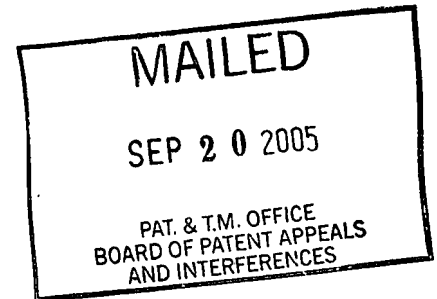
Patent Interference 104,772

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IAN FRAZER and JIAN ZHOU (deceased),  
(Application 08/185,928)

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Patent Interference 104,773



Before McKelvey, Senior Administrative Patent Judge, and Lane, Tierney, Nagumo, and Moore, Administrative Patent Judges.

Lane, Administrative Patent Judge.

**Decision - Rose Priority Date - Bd.R. 125(a)**

This is a decision on priority. Oral argument was heard on 30 June 2005, before a court reporter. Mr. Michael L. Goldman, Esq., argued for Rose.

Initial Observations

The subject matter involved in six related, but separate, Interferences 104,771 through 104,776 involves complicated biotechnology. At the outset of each interferences, the parties were advised that it would be helpful if presentations could be made using "plain English" (Paper 3). Instead, counsel for the parties have all elected to present their respective cases (both testimony and briefs) in large measure using "biotechese". We have not been able to find that any attempt was made by the parties to present a useful glossary of terms referenced directly in the briefs. We have also not been able to find any attempt to have a witness explain the technology in more basic terms. We have not been able to find in a brief a "plain English" explanation of the subject matter involved. In short, there was no attempt to educate the board in simple terms on the technology involved. We do not know why the parties basically chose to ignore Paper 3.

If the kind of exposition we are asking for were easy to write, we probably would not need to ask parties to read and comply with ¶ 43 ("Reliance on scientific tests and data") of the Standing Order (Paper 2). The study and practical applications of complex subjects leads, necessarily, to sophisticated, technical concepts, which tend to be expressed in sophisticated,

technical language. Concepts that have been reduced to things that are "patentable subject matter," however, can usually be explained to an audience in terms that explain the concepts while avoiding the technical jargon. Such explanations are not "dumbing down" the subject matter. The lack of a plain English technical background has made the case difficult to decide. Examples follow.

### **Rose**

The Rose claims require that L1 protein in virus-like particles be recognized by sera obtained from (human) patients exposed to certain viruses. What, exactly, are "sera"? What is in them as a result of exposure to a virus and what else might be present? What tests are done to see if the L1 protein is "recognized"? What does the recognition imply about the shape of the L1 protein, and why?

### **Lowy**

The Lowy claims call for capsids or virus-like particles capable of inducing high-titer neutralizing antibodies. What is a neutralizing antibody? How are titers measured in the laboratory, and when is a titer a "high titer"? How does one determine that an antibody is neutralizing?

### **Schlegel**

The Schlegel claims call for L1 protein that "exhibits the same conformation" as the L1 protein on the surface of an intact human papillomavirus. Many of its proofs involve a certain kind of "ELISA" measurement. What is actually measured? What is the significance of what is measured?

## **Frazer**

Frazer, due to the nature of its case, does not offer proofs for priority based on laboratory notebooks or the outcome of particular experiments. But its case requires that we understand the descriptions in its specifications and printed publications of the results of recombinant DNA technology, the production of proteins, and the assembly of proteins into particles resembling viruses.

A number of questions arose as we considered the laboratory experiments, measurements, and technical arguments on which the parties relied to prove conception or actual reduction to practice. How was the experiment done? What was actually measured? How reliable is the measurement? What controls ought to be done? Why? What is the level of the signal compared to the noise? How reproducible is the assay? How do the measurements relate to the conclusions the moving party would have us draw from its experiments? Why is the movant's proposed explanation the most likely explanation? What else could have led to the same result? These are the types of questions that ¶ 43 of the Standing Order indicates should be explained. We often found ourselves asking these questions as we sought to resolve the issue of priority in this interference. Seldom, however, could we find a simple, straightforward explanation in the briefing or in the record. Perhaps the parties assumed--erroneously--that we knew all about the experiments. What is absolutely plain is that all parties simply did not comply with the provisions of ¶ 43 of the Standing Order (Paper 2, page 30).

As a result, we have spent a good amount of time searching the record for the teachings we requested in ¶ 43 of the Standing Order. We have spent additional time assuring ourselves

that our understanding, expressed in plain English, is accurate. We have attempted to summarize the major features of the involved technology for the general reader in Appendix I, which is attached to this decision. We remain somewhat nonplused that the parties would provide so little guidance to the technical foundations of their cases.

As indicated during oral argument during the priority phase, we had hoped to have final decisions entered in these six interference on or before 15 August 2005. Instead, final decisions are being entered about a month later. The "delay" in entering final decisions in large measure can be attributed to the lack of a "technical education" in "plain English" by each of the parties.

In future cases, our hope is that parties take the time to educate the board in "plain English" on the nature of the technology involved in an interference.

## **I. Introduction**

This interference is one of six related interferences<sup>1</sup> among four parties. The interferences primarily relate to the principal protein of the coat of papillomaviruses, the "L1" protein, which has been proposed as a vaccine against infection by papillomaviruses. Certain papillomaviruses have been implicated as a causative agent in cervical cancers, although most papillomaviruses merely cause warts and similar nonmalignant growths in a wide variety of animals. Papillomaviruses, however, are species and tissue specific. This means, for example, that a human papillomavirus ("HPV") that infects the cervix will not reproduce in the skin of cattle. Consequently, it is difficult to grow large quantities of papillomaviruses in a test animal and to extract the viruses or the viral proteins to make and test vaccines. The advent of

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<sup>1</sup> The six interferences are 104,771 – 104,776. The parties, in increasing order of seniority, are Rose, Lowy, Frazer, and Schlegel.

recombinant genetic techniques led to the hope that proteins characteristic of the virus could be produced in large quantities, free of the viral genome. Such proteins, if they stimulated a subject's immune system to produce antibodies against the virus, would be useful as vaccines and diagnostic agents. Because they could be produced free of the viral genome, the risk of infecting patients with a virus that could lead to cancer would be minimized.

## **II. Findings of fact**

The record supports the following findings of fact, as well as any other findings of fact set forth in the opinion, by at least a preponderance of the evidence.

1. Of the six related interferences, Rose is involved in the following:

104,771(Rose v. Lowy) ('771),

104,772 (Rose v. Schlegel) ('772), and

104,773 (Rose v. Frazer) ('773).

### *Interference 104,771*

#### Rose

2. Rose's involved 08/207,309 (309) application was filed 7 March 1994.
3. The 309 application is entitled "Production of human papillomavirus capsid protein and virus-like particles."
4. The named inventors of the involved 309 application are Robert C. Rose, William Bonnez, and Richard C. Reichman.
5. The 309 application was filed as a continuation-in-part of application 08/028,517 (517), which was filed 9 March 1993.
6. Rose has been accorded benefit for priority of the 517 application.

7. The University of Rochester and Strong Memorial Hospital are Rose's real parties-in-interest. MedImmune, Inc. and SmithKline Beecham PLC are licensees.

Lowy

8. Lowy's involved application, 08/484,181 (181), was filed 7 June 1995.
9. The 181 application was filed as a division of application 07/941,371 (371), filed 3 September 1992.
10. Lowy has been accorded the benefit for priority of the 371 application.
11. The title of the 181 application is "Self-assembling recombinant papillomavirus capsid proteins."
12. The named inventors of the 181 application are Douglas R. Lowy, John T. Schiller, and Reinhard Kirnbauer.
13. The real parties in interest of the 181 application are the assignee, the United States of America, as represented by the Department of Health and Human Services. MedImmune, Inc. and Merck & Co., Inc. are licensees.

The count

14. The sole count in the '771 interference is as follows:

A composition of matter according to any of claims 42, 43, or 65 of Rose or a method according to any of claims 44, 56, or 71 of Rose or a composition of matter according to either of claims 48 or 49 of Lowy.

15. Rose claim 42 reads:

An isolated non-infectious human papillomavirus virus-like particle or capsomere comprising an HPV-11 L1 capsid protein sequence or an HPV-6 L1 capsid protein sequence which is conformationally correct and is recognized by antibodies present in sera obtained from HPV-11 or HPV-6 infected human patients,

respectively.

16. Rose claim 43 reads:

An isolated non-infectious, recombinant human papillomavirus virus-like particle or capsomere produced according to the method comprising: infecting a cell with a recombinant expression vector containing a human papillomavirus type-6 L1 capsid protein coding sequence or a human papillomavirus type-11 L1 capsid protein coding sequence under conditions facilitating expression of said L1 capsid protein, thereby producing a non-infectious human papillomavirus virus-like particle or capsomere comprising a human papillomavirus type-6 L1 capsid protein sequence or a human papillomavirus type-11 L1 capsid protein sequence, which is conformationally correct and is recognized by antibodies present in sera obtained from human papillomavirus type-6 infected human patients or human papillomavirus type-11 infected human patients, respectively, and isolating said particle.

17. Rose claim 65 reads:

An isolated non-infectious human papillomavirus virus-like particle or capsomere comprising a human papillomavirus L1 capsid protein which is conformationally correct and is recognized by antibodies present in sera obtained from human patients infected with the human papillomavirus.

18. Rose claim 44 reads:

A method of producing an isolated non-infectious human papillomavirus virus-like particle or capsomere in a cell comprising: transfecting a cell with a recombinant expression vector containing a human papillomavirus type-6 capsid protein coding sequence or a human papillomavirus type-11 capsid protein coding sequence under conditions facilitating expression of said capsid protein, thereby producing a non-infectious papillomavirus virus-like particle or capsomere comprising a human papillomavirus type-6 L1 capsid protein sequence or a human papillomavirus type-11 L1 capsid protein sequence, which is conformationally correct and is recognized by antibodies present in sera obtained from human papillomavirus type-6 infected patients



or human papillomavirus type-11 infected patients, respectively, and isolating said particle.

19. Rose claim 56 reads:

A method of producing an isolated non-infectious human papillomavirus virus-like particle or capsomere in an insect cell comprising: cloning a human papillomavirus L1 capsid protein coding sequence selected from the group consisting of a human papillomavirus type-6 L1 capsid protein coding sequence and a human papillomavirus type-11 L1 capsid protein coding sequence into a baculovirus transfer vector, co-transfecting insect cells with said baculovirus transfer vector and *Autographa californica* nuclear polyhedrosis virus genomic DNA; recovering recombinant baculoviruses; and infecting said insect cells with said recombinant baculoviruses under conditions facilitating expression of the capsid protein, thereby producing a non-infectious papillomavirus virus-like particle or capsomere comprising a human papillomavirus type-6 L1 capsid protein or a human papillomavirus type-11 L1 capsid protein, which is conformationally correct and is recognized by antibodies present in sera obtained from human papillomavirus type-6 infected patients or human papillomavirus type-11 infected patients, respectively, and isolating said particle.

20. Rose claim 71 reads:

A method of producing an isolated non-infectious human papillomavirus virus-like particle or capsomere in a cell comprising: transfecting a cell with a recombinant expression vector containing a human papillomavirus capsid protein coding sequence under conditions facilitating expression of said capsid protein, thereby producing a non-infectious papillomavirus virus-like particle or capsomere comprising an L1 capsid protein for the human papillomavirus, which is conformationally correct and is recognized by antibodies present in sera obtained from patients infected with the human papillomavirus.

21. Lowy claim 48 reads:

Isolated papillomavirus capsids comprising an L1 polypeptide which contains at least one conformational epitope and is capable

of inducing high-titer neutralizing antibody, produced by the method comprising: permitting a genetic construct, comprising a papillomavirus L1 gene, to direct recombinant expression and self-assembly of papillomavirus capsids comprising the L1 polypeptide in a transformed eukaryotic host cell; and isolating said self-assembled capsids.

22. Lowy claim 49 reads:

Isolated papillomavirus-like particles comprising an L1 polypeptide which contains at least one conformational epitope and is capable of inducing high-titer neutralizing antibody, produced by the method comprising: permitting a genetic construct, comprising a papillomavirus L1 gene, to direct recombinant expression and self-assembly of papillomavirus-like particles comprising the L1 polypeptide in a transformed eukaryotic host cell; and isolating said self-assembled particles.

23. Lowy claim 48 that makes up the count was construed to read on naturally occurring virions in interference 104,775 ('775, Paper 149 at 66 and 70).

24. In interference 104,775, Lowy claim 48 was held to be unpatentable to Lowy. ('775, Paper 149 at 70).

25. All Rose claims, namely 35-37, 41<sup>2</sup>-45, 48, 50, 52-57, 59, 61-65, 67-72, 75-77, 79-89 and 91, correspond to the count. ('771, Paper 107 at 2).

26. All Lowy claims, namely claims 34-49, have been designated as corresponding to the count. (Paper 107 at 2).

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<sup>2</sup> In the declaration of the interference (Paper 1), Rose claim 41 was inadvertently left out of the list of Rose claims designated as corresponding to the count. The interference was redeclared with claim 41 designated as corresponding to Count 1. (Paper 33; Paper 128.)

27. In the Form 850 in Interference 103,929,<sup>3</sup> the examiner has indicated that Lowy claims 34-47 are otherwise unpatentable. (Paper 1 at 6 n.3).

*Interference 104,772*

Rose

28. The Rose involved application is described above.

Schlegel

29. Schlegel's involved application, 08/216,506 (506) was filed 22 March 1994.
30. Schlegel's involved application is entitled "Human papillomavirus vaccines containing conformationally correct L1 capsid proteins."
31. The named inventors of the 506 application are C. Richard Schlegel and A. Bennett Jensen.
32. The 506 application was filed as a continuation of the 07/903,109 ('109) application, which was filed 25 June 1992.
33. Schlegel was accorded the benefit for priority of the 109 application.
34. The Georgetown University School of Medicine is Schlegel's real party-in-interest. MedImmune, Inc. and SmithKline Beecham PLC are licensees.

The count

35. The sole count of the '772 interference is as follows:

A composition of matter according to any of claims 42, 43 or 65 of Rose or a method according to any of claims 44, 56 or 71 of Rose or a composition of matter according to any of claims 1, 12, 50 or 64 of Schlegel or a method

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<sup>3</sup> Interference 103,929, a four party interference involving the same subject matter and same parties as interference 104,771 through 104,776, was administratively terminated in favor of pair-wise interferences 104,771 through 104,776.

according to any of claims 19, 53 or 55 of Schlegel.

36. The alternatives of the count made up of Rose claims are the same as in the '771 interference.

37. The Schlegel claims that are alternatives of the count are as follows:

38. Schlegel claim 1 reads:

An isolated recombinantly produced human papillomavirus (PV) L1 protein, wherein said protein reproduces the antigenicity and exhibits the same conformation as an L1 major capsid protein expressed on the surface of intact human papillomavirus virions.

39. Schlegel claim 12 reads:

A vaccine for the prevention of papillomavirus infection, said vaccine comprising at least one recombinantly produced human papillomavirus (PV) L1 protein, which protein reproduces the antigenicity and exhibits the same conformation as an L1 major capsid protein expressed on the surface of intact human papillomavirus virions.

40. Schlegel claim 19 reads:

A method for protecting a human against a papillomavirus infection, said method comprising administering a therapeutically effective amount of a vaccine, wherein said vaccine comprises at least one isolated recombinantly produced human papillomavirus (PV) L1 protein wherein said protein reproduces the antigenicity and exhibits the same conformation as an L1 major capsid protein expressed on the surface of intact human papillomavirus virions.

41. Schlegel claim 50 reads:

A vaccine for the prevention of papillomavirus infection, said vaccine consisting essentially of at least one isolated recombinant papillomavirus (PV) L1 protein, which protein reproduces the antigenicity and exhibits the same conformation as an L1 major capsid protein expressed on the surface of intact human papillomavirus virions.

42. Schlegel claim 53 reads:

A method of protecting a human against a papillomavirus infection, said method comprising administering a therapeutically effective amount of a vaccine according to claim 50.

43. Schlegel claim 55 reads:

A method for protecting a human against a human papillomavirus infection, comprising administering to a human subject a therapeutically effective amount of a vaccine according to claim 52.

44. Schlegel claim 52 reads:

The vaccine of claim 50 wherein the human papillomavirus is either HPV-6 or HPV-11a.

45. Schlegel claim 64 reads:

An isolated recombinantly produced human papillomavirus (HPV) L1 protein, comprising a protein which specifically binds to conformational antibodies which react with an L1 protein expressed on the surface of an intact HPV virion.

46. All the Rose claims correspond to the Count. ('772, Paper 61 at 62).

47. Schlegel claims 1-3, 12-14, 16, 19, 23-25, 46, 47, 50, 52, 53, 55-60, 62 and 64 correspond to the count. ('772, Paper 61 at 2).

48. The examiner setting up the interference has indicated that Schlegel claims 10, 11, 15, 17, 18, 21, 22, 26, 51, 54, 61, 63, 65 and 66 are otherwise unpatentable.

49. During interference 104,776, Schlegel claims 1 and 64 were construed to read on an isolated native HPV virion. ('776, Paper 175 at 93).

50. Schlegel claims 1 and 64 were held to be unpatentable to Schlegel during the 104,776 interference. ('776, Paper 176 at 93).

*Interference 104,773*

Rose

51. The involved Rose application is as described above.

Frazer

52. Frazer involved 08/185,928 (928) application was filed 19 January 1994 as the national stage (35 U.S.C. § 371) of PCT Application PCT/AU92/00364 (PCT), filed 20 July 1992
53. The 928 application is entitled "Papillomavirus vaccines".
54. Frazer has been accorded the benefit for priority of the PCT application.<sup>4</sup>
55. The named inventors of the 928 application are Ian Frazer and Jian Zhou (deceased, 1999).
56. Frazer's real party-in-interest is CSL Limited (Australia) and University of Queensland (Australia). Merck & Co., Inc., is a licensee.

The count

57. The sole count of the '773 interference is as follows:

A composition of matter according to any of claims 42, 43 or 65 of Rose or a method according to any of claims 44, 56 or 71 of Rose or a composition of matter according to claims 67 or 91 of Frazer or a method according to either of claims 65, 89 or 96 of Frazer.

58. The alternatives of the count which are Rose claims are the same as in the '771 and '772 interferences.
59. Frazer claim 65 reads:

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<sup>4</sup> Frazer was accorded priority benefit of Australian application PK 7322 (Australian), filed 19 July 1991 but as a result of the Decision on Preliminary Motions, lost the priority benefit. (Paper 197 at 119).

A method of making a papillomavirus virus-like particle, which method comprises: constructing a recombinant DNA molecule that contains a sequence encoding a papillomavirus L1 protein; transfecting a host cell with the recombinant DNA molecule; expressing papillomavirus L1 protein in the host cell; and obtaining papillomavirus virus-like particles from the transfected host cell; wherein the papillomavirus is not HPV 16.

60. Frazer claim 67 reads:

A papillomavirus virus-like particle made by the method of claim 65.

61. Frazer claim 91 reads:

Papillomavirus L1 protein and L2 protein made by the method of claim 89.

62. Frazer claim 89 reads:

A method of making papillomavirus L1 protein and L2 protein, which method comprises: constructing a recombinant DNA molecule that contains a sequence encoding a papillomavirus L1 protein and a sequence encoding a papillomavirus L2 protein; transfecting a host cell with the recombinant DNA molecule; expressing papillomavirus L1 protein and L2 protein in the host cell; and obtaining papillomavirus L1 protein and L2 protein from the transfected host cell.

63. Frazer claim 97 reads:

A method of producing anti-papillomavirus antibodies in an animal comprising administration of a papillomavirus virus-like particle to the animal.

64. All of Rose's claims correspond to the count. ('773, Paper 200 at 2-3).

65. All of Frazer's claims, namely claims 65–80, and 89–100, correspond to the count. ('773, Paper 200 at 2-3).

66. In the decision on preliminary motions, it was held that the virus-like particules (VLPs) lacking conformational correct epitopes do not fall within the scope of the count. ('773,

Paper 197 at 106)<sup>5</sup>

67. In particular, the utilities of diagnostics and immunization disclosed by Frazer require the presence of conformational epitopes on the VLPs that are the same as conformational epitopes on the capsids of native virions.
68. During interference 104,775, Frazer claim 91 was construed to read on an isolated native HPV virion. ('775, Paper 149 at 70).
69. Frazer claim 91 was held to be unpatentable to Frazer during the 104,775 and 104,776 interferences. ('775, Paper 149 at 70 and '776, Paper 175 at 128).<sup>6</sup>

*Rose's pre-October 1991 activity*

70. According to Rose, Dr. Rose first got the idea of making VLPs after attending a meeting of the American Society for Virology (ASV) held in Utah in July, 1990 where the formation of HIV-2 VLPs was discussed. (Paper 143<sup>7</sup> at 14).
71. Thereafter, Rose is said to have presented a list of potential research projects to his thesis advisor and coinventor, Dr. Richard C. Reichman. (Exh. 4165)
72. The list included a project, i.e., "Project 3 ", which would be an attempt to concurrently express three HPV-11 proteins within the same Sf-9 insect cell such that it would be

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<sup>5</sup> Our decision was in the context of a motion to deny Frazer priority benefit. While only claims 65 of Rose and 89, 91, and 97 of Frazer were discussed specifically, the reasoning applies to all the claims that make up the count.

<sup>6</sup> Claim 89 also was held to be unpatentable to Frazer but that holding was withdrawn on reconsideration. (Paper 229 at 12).

<sup>7</sup> Rose's priority brief is paper 143 in the '771 interference, paper 72 in the '772 interference, and paper 211 in the '773 interference. Rose's briefs are in large part the same in each interference. For convenience we refer only to the paper number accorded to the brief in the '771 interference.



“possible” that the HPV capsid proteins would self-assemble into VLPs. (Exh. 4165 at 3).

73. In its brief Rose stated that “as of August 27, 1990, the concept of the invention was complete” (Paper 143 at 16).
74. Rose relies upon the testimony of Dr. Josef Sapp, who is said to be “an expert in the field of papillomaviruses and the development of vaccines for them, particularly with respect to the field of recombinantly producing HPV VLPs and evaluating such products serologically.” (Exh. 4142 at ¶ 6).
75. Dr. Sapp testified that, given that Rose had the necessary capsid protein encoding nucleic acid, baculovirus and Sf-9 cells by 27 August 1990, Rose “had what was necessary to proceed with recombinantly producing and testing HPV VLPs, which would *hopefully* have the conformation of native virions, making the VLPs useful for vaccines and diagnostics” as of that date. (Exh. 4142 at ¶ 9, emphasis added).
76. At oral hearing, Rose indicated that, despite arguments in its principal briefs, it is no longer arguing that the August 1990 work is a conception or a reduction to practice of the invention of the count. (TX<sup>8</sup> at 52-53).
77. In each interference, the preliminary statement filed by Rose indicates that “the date on which the invention was first disclosed by the inventors to another person is on or before July 25, 1991.” (‘772, Paper 22 at 2).

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<sup>8</sup> The transcript is paper 192 in the ‘771 interference, paper 98 in the ‘772 interference, and paper 275 in the ‘773 interference.

*The October 1991 activity*

78. At oral hearing, Rose indicated that it would be relying upon its October 1991 activity as an actual reduction to practice or at least a conception of an embodiment within the scope of the count. (TX at 52-53).
79. According to Rose, as of early October 1991, Dr. Rose had produced, recombinantly, HPV-6 L1 capsid protein alone and HPV-6 L1 and L2 capsid proteins together, using a baculovirus expression vector and Sf-9 insect cells.
80. Rose states that on October 8, 1991, Dr. Rose analyzed results of a radio-immunoprecipitation assay (RIPA) which indicated that the HPV-6 capsid proteins, recombinantly produced by Dr. Rose, reacted with R8-366 antiserum. (Paper 143 at 17-18).
81. According to Rose, the RIPA results demonstrate that the recombinantly produced capsid proteins are conformationally correct.
82. The R8-366 antiserum was obtained from rabbits infected with native HPV-11 virions.
83. Therefore the October 1991 RIPA results showed reactivity between what were said to be HPV-6 VLPs and anti-sera from rabbits infected with HPV-11.

Corroboration

84. Rose states that “there is substantial corroboration of these events” and directs us to the following:
- (a) the notebooks of Dr. Rose (Exhs. 4128, 4129, 4131, 4132, 4147 and 4148) ,
  - (b) the testimony of the inventors (Exh. 4136 (Dr. Bonne) and Exh. 4144 (Dr. Reichman)),

- (c) the testimony of Dr. Rose's laboratory partner, Caroline Harvey (Exh. 4143)
- (d) the testimony of Dr. Robert Garcea to whom Dr. Rose sent material for electron microscopic analysis (Exh. 4145),
- (e) the testimony of Marlene Shero (Exh. 4206), a research support specialist who performed electron micrograph experiments (Exh. 4206),
- (f) the testimony of Martha Smith, a laboratory technician in the Photography Unit at the University of Rochester (Exh. 4144).

(Paper 143 at 34-35).

*Dr. Rose's notebooks:*

85. Dr. Rose's notebooks appear to be of the "loose-leaf" type and most, if not all, of the notebook pages, while dated, are not signed or initialed by Dr. Rose or a witness.

*The coinventor testimony:*

86. Rose does not direct us to any particular portions of the testimony of the coinventors that Rose contends would corroborate Dr. Rose's testimony.

*Caroline Harvey's testimony:*

87. Rose directs us to ¶¶ 4-6, and 8 of Ms. Harvey's declaration.
88. According to these paragraphs of Ms. Harvey's testimony she worked in the same laboratory as Dr. Rose from 1990 to 1992 where she was generally aware of, and sometimes assisted in, Dr. Rose's efforts to produce HPV L1 in insect cells using the baculovirus expression system, verify the presence of VLPs using electron microscopy, and test the immunological characteristics of the recombinantly produced L1.
89. Rose has not directed us to a portion of Ms. Harvey's declaration indicating that she was

aware of the RIPA that Dr. Rose is said to have performed and analyzed in early October of 1991.

*Dr. Garcea's testimony:*

90. Rose directs us to ¶¶ 9 and 10 of Dr. Garcea's declaration.
91. Dr. Garcea's testimony indicates that he and Dr. Rose entered into an agreement where he would be responsible for the structural analysis of HPV VLPs primarily using electron microscopy and Dr. Rose would be responsible for the immunological analysis of HPV VLPs.
92. According to Dr. Garcea, on 16 October 1991, he received a package from Dr. Rose along with a letter explaining that the package contained recombinant baculovirus stocks expressing: (1) the complete L1 coding sequence of HPV-6b, (2) the complete L2 coding sequence of HPV-6b, and (3) a 735 bp HPV-11 E1^E4 cDNA.
93. We have not been directed, in Rose's principal brief, to evidence indicating that Dr. Garcea confirmed the contents of the package.
94. Dr. Garcea testified that he understood that Dr. Rose wanted Sf-9 cells to be infected with these stocks to grow samples that could then analyzed by electron microscopy.
95. Dr. Garcea testified he has "not been able to find that these samples were grown or that I analyzed them by electron microscopy." (Exh. 4145 at ¶ 11).

*Marlene Shero's testimony:*

96. Rose directs us to ¶¶ 4-7 of Ms. Shero's declaration.
97. According to Ms. Shero, in July and September of 1991, Dr. Rose sent her a number of letters, copies of which are found in Dr. Rose's laboratory notebook. (Exh. 4130 at 77,

79, 80-82, and 85).

98. Ms. Shero also testified that she sent a letter to Dr. Bonnez in December of 1991, a copy of which is also found in Dr. Rose's laboratory notebook. (Exh. 4130 at 66).
99. These letters seem to relate to Dr. Rose's or Dr. Bonnez's requests to have Ms. Shero prepare electron micrographs of samples of Sf-9 cells "that were believed to express baculovirus and/or papillomavirus-like particles." (Exh. 4206 at ¶ 6).

*Martha Smith's testimony:*

100. Rose directs us to ¶¶ 4-19 of Ms. Smith's declaration.
101. According to these portions of Ms. Smith's testimony, copies of envelope fronts found in Dr. Rose's laboratory notebook indicate to her that Dr. Rose or Dr. Bonnez brought in "orders" for photographing to the Photograph Unit at the University of Rochester Medical Center at various times from September of 1990 through September of 1992.
102. The envelope fronts appear to have at least a serial number, a date, and an inventor's name, usually Dr. Rose, printed thereon. (See, e.g., Exh. 4128 at 25).
103. Ms. Smith testified that she recognizes her handwriting or the handwriting of her husband on certain envelope copies and that the handwriting thereon indicates that Dr. Rose or Dr. Bonnez brought in an "order" for photographing and that the "order" was assigned a certain serial number.
104. While Rose did not direct us to this portion of Ms. Smith's testimony in its principal briefs, Ms. Smith also testified that it was her practice to stamp the assigned serial number on the back of each photograph printed for a particular order. (Exh. 4144 at ¶ 3).
105. Rose has not directed us to a copy of a photograph of the RIPA results Dr. Rose is said to

have obtained in October of 1991.

*The July 1992 activity*

106. According to Rose, a second actual reduction to practice of the invention of the counts occurred on 15 July 1992. (Paper 143 at 39).
107. Rose states that in June of 1992 Dr. Rose sent recombinant baculovirus to Dr. Garcea, such that Dr. Garcea could infect Sf-9 cells and analyze the cells using high powered electron microscopy.
108. According to Rose, as of July 15, 1992, Rose had confirmation that HPV VLPs of the correct size and symmetry had been created based on the electron micrographs created by Dr. Garcea.
109. Rose has submitted testimony indicating that visualization of particles, without serological testing, does not show the presence of conformationally correct epitopes. (e.g., Exh. 4145 at ¶ 19, discussed *infra* at FF 116).
110. Rose relies upon Dr. Garcea's and Carrie Harvey's testimony to corroborate the July 1992 electron microscopy work. (Paper 143 at 40-44).
111. Dr. Garcea's testimony indicates that he spoke with Dr. Rose on 15 July 1992 regarding the results of the electron microscopy analysis of the HPV-11 VLPs.
112. Dr. Garcea testified that he told Dr. Rose that he had concluded that the Sf-9 cells infected with Dr. Rose's recombinant vAcHPV-11 L1 expressed VLPs of the correct size and symmetry[[to be VLPs]. (Exh. 4145 at ¶ 20).
113. The portion of Ms. Harvey's testimony pointed out to us by Rose indicates that Dr. Rose showed Ms. Harvey electron micrographs and told Ms. Harvey that he had received

electron micrographs that he thought “clearly showed VLPs.” (Exh. 4143 at ¶ 21).

114. According to Ms. Harvey, Dr. Rose told her this “in 1992”. (Exh. 4143 at ¶ 21).

115. Rose acknowledges that “serological analyses, such as RIPAs, are central to determining whether a capsid protein or capsid proteins are conformationally correct” and that electron microscopy is useful “to confirm positive serological results”. (Paper 143 at 40).

116. According to Dr. Garcea:

The fact that the electron micrographs showed HPV VLPs of an appropriate size range and a likely T=7 symmetry indicated to me that baculoviruses expressing L1 sent to me by Robert Rose had expressed HPV VLPs. *I understood, however, that immunological work would be needed to confirm that the particles had epitopes that generated immune responses similar to a native HPV viruses [sic].*

(Exh. 4145 at ¶ 19, emphasis added).

117. Dr. Garcea’s testimony above is similar to that of Dr. Sapp that “serological analyses are central to demonstrating to those skilled in developing vaccines and diagnostics for human papillomaviruses that a particular human papillomavirus capsid protein product is conformationally correct.” (Exh. 4142 at ¶ 33).

118. According to Dr. Sapp, while electron microscopy is not required to show conformational correctness, an electron micrograph showing products having the same shape as a native VLP virion is useful in confirming positive serological results. (Exh. 4142 at ¶ 33).

119. Dr. Sapp states that electron micrographs that do not show a product having the appearance of native HPV virion suggests that the protein is not conformationally correct. (Exh. 4142 at ¶ 33).

*The August/September 1992 activity*

120. Rose argues that a further actual reduction to practice occurred on 10 August 1992 when Rose successfully tested its VLPs with mouse and rabbit antisera in an immuno-dotblot assay. (Paper 143 att 45).
121. Rose argues that a still further actual reduction to practice occurred “no later than 20 September 1992”, when it received results from an immunodotblot assay of its VLPs performed using human sera obtained from HPV-infected patients.
122. Rose relies upon Dr. Rose’s testimony and laboratory notebook to show that Dr. Rose completed the alleged actual reduction to practice.
123. According to Rose, Dr. Rose’s laboratory notebooks are corroborated by:
  - (a) exhibits showing the actual test results (Exh. 4128 at 20-21, 26-27, and 51-54),  
and
  - (b) the testimony of Martha Smith (Exh. 4144).

*Dr. Rose’s notebook:*

124. Rose directs us to certain portions of Dr. Rose’s laboratory notebook that contain what appear to be photographs of test results.
125. In particular, it appears that certain test results were photographed and a copy of the photograph is what is said to appear in Dr. Rose’s notebook. (See, e.g., Exh. 4128 at 20 and 26).
126. Much of, if not all of, Dr. Rose’s notebook is unwitnessed.
127. While in its principal briefs Rose did not direct us to these portions of Dr. Rose’s notebook, we note that following certain pages to which we were directed, are pages



containing, in unclear print, the words "PHOTOGRAPHY UNIT" and a six digit number. (e.g., "925506 "at Exh. 4128 at 20A).

*Ms. Smith's testimony:*

128. Rose directs us to ¶¶ 18-19 of Ms. Smith's declaration.
129. According to these portions of Ms. Smith's testimony, copies of envelope fronts found in Dr. Rose's laboratory notebook indicate that Dr. Rose brought in a certain order for photographing to the Photograph Unit at the University of Rochester Medical Center on 31 August 1992 and again on 21 September 1992.
130. Ms. Smith testified that she recognizes her handwriting on copies of the envelope fronts, each of which appear to have at least a serial number, a date, and an inventor's name, usually Dr. Rose, printed thereon (see, e.g., Exh. 4129 at 131), and that the handwriting on the envelope fronts indicates that Dr. Rose brought in "an order" for photographing and that the order was assigned a certain serial number.
131. While Rose did not direct us to this portion of Ms. Smith's testimony, Ms. Smith also testified that it was her practice to stamp the assigned serial number on the back of each photograph printed for a particular order. (Exh. 4144 at ¶ 3).
132. Rose did not direct us to testimony from Ms. Smith indicating that she remembered seeing any particular result.

*Alternative reductions to practice*

133. Rose argues that it can satisfy the count by showing that it produced, on or before 21 July 1991, an embodiment falling within the scope of an opponent's claim that is an alternative of the count. (See, e.g., Paper 143 at 54).
134. According to Rose, the Board has interpreted these claims of the counts as reading on an isolated native HPV virion.

*Diligence*

135. At oral argument, Rose stated that its diligence began in February of 1992. (TX at 23:8:24:2).
136. Dr. Rose has testified that he was continuously working toward producing conformationally correct VLPs from the end of February of 1992 until October of 1992. (Exh. 4127 at ¶¶ 195-306).

*Electron microscopy:*

137. According to Dr. Rose, he sent vials containing recombinant samples of L1 supernatant, L2 supernatant, and E1^E4 supernatant along with samples of certain antisera on 18 June 1992. (Exh. 4127 at ¶ 250).
138. Dr. Rose testified that he spoke with Dr. Garcea on 15 July 1992 "about his visualization of what appear to be perfectly formed HPV particles in vAcH11L1-infected cells." (Exh. 4127 at ¶ 253).

*The seminar:*

139. Dr. Rose testified that he presented the results of his work on HPV VLPs at a department seminar he conducted on 24 September 1992. (Exh. 4127 at ¶ 300; Paper 143 at 72).
140. Dr. Rose testified that “[i]n particular, I showed the recent dotblot results and electron micrograph images showing the HPV-11 VLPs.” (Exh. 4127 at ¶ 300).
141. According to Rose, Dr. Rose’s testimony regarding diligence is corroborated by:  
  
the testimony of Dr. Garcea  
  
the testimony of Ms. Smith, and  
  
the testimony of Ms. Harvey.

*Dr. Garcea’s testimony:*

142. Rose directs us to ¶¶ 13-15, and 20 of Dr. Garcea’s testimony. (See FF 11-112, *supra*).
143. Dr. Garcea’s testimony indicates that under his direction HPV protein samples were prepared from the vials of HPV DNA sent to him by Dr. Rose. (Exh. 4145 at ¶13).
144. Dr. Garcea testified that electron micrographs of the samples were taken on 8 July 1992, 10 July 1992, and 3 August 1992. (Exh. 4145 at ¶¶ 13-15).
145. Dr. Garcea testified that he spoke to Dr. Rose on 15 July 1992 and told him that he had analyzed the electron micrographs and concluded that the samples contained particles of the correct size and symmetry [to be VLPs of HP]. (Exh. 4145 at ¶ 20).

*Ms. Smith's testimony:*

146. Rose directs us to ¶¶ 15-19 of Ms. Smith's testimony. (See FFs 100-105 and 128-132, *supra*).
147. According to these portions of Ms. Smith's testimony, copies of envelopes fronts found in Dr. Rose's laboratory notebook indicate that Dr. Rose brought in a certain order for photographing to the Photograph Unit on each of the following dates: 15 July 1992, 27 July 1992, 5 August 1992, 31 August 1992, and 21 September 1992. (Exh. 4144 at ¶¶ 15-19).

*Ms. Harvey's testimony:*

148. Rose directs us to ¶ 28 of Ms. Harvey's testimony.
149. Ms. Harvey testified that she attended a student seminar in September of 1992 where Dr. Rose showed copies of dot blot assays involving sera from diagnosed condyloma patients together with controls drawn from priests and nuns.
150. Ms. Harvey testimony indicates that the assays showed that a majority of the patient sera had reacted positively to "the VLPs" and the controls "were negative."

### **III. Discussion**

As the junior party in each of the three interferences to which it is a party, Rose has the burden of proving priority as to each of Lowy, Frazer, and Schlegel. Bd.R. 121(b). Rose argues that it was the first to conceive an invention of each count and that it either reduced the invention to practice prior to the other parties or was diligent in reducing its invention to practice.

Rose has not shown by a preponderance of the evidence that it either conceived or reduced to practice an invention of the count prior to the priority benefit dates of any of its

opponents. In particular, Rose has not directed us to evidence sufficient to corroborate the testimony and unwitnessed laboratory notebooks of Dr. Rose upon which Rose relies to show conception and actual reduction to practice. Even if Rose had shown an earlier conception, Rose has not directed us to evidence sufficient to corroborate the testimony and unwitnessed laboratory notebooks of Dr. Rose upon which Rose relies to show diligence.

A. The counts

1. The '771 count:

The sole count of the '771 interference is as follows:

A composition of matter according to any of claims 42, 43 or 65 of Rose or a method according to any of claims 44, 56 or 71 of Rose or a composition of matter according to either of claims 48 or 49 of Lowy.

(FF 14).

Of the claims of Rose that make up alternatives of the count, claim 65 appears to be the broadest and is directed to isolated non-infectious, recombinant human papillomavirus (HPV) virus-like particles (VLPs) or capsomeres comprising a HPV L1 capsid protein sequence. The claim requires that the VLPs or capsomeres be conformationally correct and be recognized by antibodies present in sera obtained from a human patient who is infected with corresponding HPV. Claim 71 is directed to a method of producing these VLPs or capsomeres by transfecting a cell with a recombinant expression vector containing an HPV capsid protein coding sequence to produce non-infectious VLPs or capsomeres comprising an HPV L1 capsid protein. The claim requires that the VLPs or capsomeres be conformationally correct and be recognized by antibodies present in sera obtained from patients infected with the HPV. Notably claim 65 requires that antibodies from human patients recognized the VLPs or capsomeres while claim 71

does not specify that the patient must be human. Our understanding of claim 71 is that, in referring back to “the” HPV in describing the infecting HPV used to obtain antisera, claim 71 requires that the VLPs or capsomeres be recognized by sera from patients infected with the same HPV serotype as the VLPs or capsomeres being produced. Rose seems to agree. (TX at 18:4-14).

Lowy claim 48 that makes up another alternative of the count was construed to read on naturally occurring virions in interference 104,775 (FF 24) and thus was found to be unpatentable to Lowy in that interference.

Lowy claim 49 is directed to isolated papillomavirus VLPs having at least one conformational epitope and capable of inducing high-titer neutralizing antibodies. Claim 49 does not require that the VLPs raise antibodies in human patients or in patients infected with PV of the same serotype as the produced VLPs.

2. The ‘772 count

The sole count of the ‘772 interference is as follows:

A composition of matter according to any of claims 42, 43 or 65 of Rose or a method according to any of claims 44, 56 or 71 of Rose or a composition of matter according to any of claims 1, 12, 50 or 64 of Schlegel or a method according to any of claims 19, 53 or 55 of Schlegel.

(FF 35).

The Rose claims that make up alternatives of the count are the same as in the ‘771 and ‘773 interference.

Schlegel claims 1 and 64 were construed to read on an isolated native HPV virion in interference 104,776. Schlegel claims 1 and 64 were held to be unpatentable to Schlegel during

the 104,776 interference. ('776, Paper 175 at 93).

3. The '773 count

The sole count of the '773 interference is as follows:

A composition of matter according to any of claims 42, 43 or 65 of Rose or a method according to any of claims 44, 56 or 71 of Rose or a composition of matter according to claims 67 or 91 of Frazer or a method according to either of claims 65, 89 or 96 of Frazer.

(FF 57).

The Rose claims that are alternatives of the count are the same as in the '771 and '772 interferences.

During interference 105,775, Frazer claim 91 was construed to read on an isolated native HPV virion. Claim 91 was held to be unpatentable to Frazer in the context of the 105,775 interference. (FFs 68 and 69).

The Frazer portion of the count is directed to papillomavirus VLPs, where the papillomavirus is not HPV-16, or L1 and L2 proteins made recombinantly. While the Frazer claims do not explicitly require conformational epitopes, we previously have held that the VLPs or L1 and L2 proteins in Frazer claims must have conformational epitopes in order to have a utility. (FFs 66 and 67 and Paper 143 at 38).

B. The relevant legal standards

1. Conception, reduction to practice, and diligence

Conception is the formation, in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice. *Coleman v. Dines*, 754 F.2d 353, 359, 224 USPQ2d 857, 862 (Fed. Cir. 1985). Conception requires both

the idea of the invention's structure and possession of an operative method of making it. *Oka v. Youssefyeh*, 849 F.2d 581,583, 7 USPQ2d 1169, 1171 (Fed. Cir. 1988). Accordingly, the inventor must have at least a reasonable expectation that the inventor can produce an invention of the count in order to establish a conception. Where the specific result of an unpredictable process is part of the count, conception cannot occur absent a reasonable expectation that the result of the process would occur. *Hitzeman v. Rutter*, 243 F.3d 1345, 1358, 58 USPQ2d 1161, 1169. (Fed. Cir. 2001).

In order to actually reduce an invention to practice, the inventor must construct the invention, i.e., construct an embodiment or perform a process that meets all the limitations of the count, and determine that the invention works for its intended purpose. *Cooper v. Goldfarb*, 154 F.3d 1321, 1327, 47 USPQ2d 1896, 1901 (Fed. Cir. 1998).

A party alleging diligence must show reasonable diligence from a date prior to its opponent's conception to the date of the party's actual or constructive reduction to practice, i.e., throughout the "critical period". *Monsanto Co. v. Mycogen Plant Sci. Inc.*, 261 F.3d 1356, 1363, 59 USPQ2d 1930, 1934 (Fed. Cir. 2001). A sufficient showing of reasonable diligence must account for the entire critical period by showing reasonable continuous activity toward a reduction to practice. *Mahurkar v. C.R. Bard, Inc.* 79 F.3d 1572, 1577, 38 USPQ2d 1288, 1290 (Fed. Cir. 1996).

## 2. Corroboration

"An inventor's testimony standing alone, is insufficient to prove conception-some form of corroboration must be shown." *Price v. Symsek*, 988 F.2d 1187, 1196, 26 USPQ2d 1031, 1036 (Fed. Cir. 1993). The inventor's testimony alone also is not sufficient to establish an actual



reduction to practice, *Cooper*, 154 F.3d at 1330, 47 USPQ2d, at 1903; or diligence, *Price*, 988 F.2d at 1196, 26 USPQ2d at 1037. The unwitnessed and uncorroborated laboratory notebook pages of an inventor generally are accorded no more weight than the inventor's testimony. *Reese v. Hurst*, 661 F.2d 1222, 1231, 211 USPQ 936, 945, (CCPA 1981). The requirement for corroboration of an inventor's testimony stems from the concern that a party claiming inventorship might be tempted to describe his actions in an unjustifiably self-serving manner in order to obtain a patent or to maintain an existing patent. *Chen v. Bouchard*, 347 F.3d 1299, 1309, 68 USPQ2d 1705, 1712 (Fed. Cir. 2003). However, "[t]here is no single formula that must be followed in proving corroboration." *Berry v. Webb*, 412 F.2d 261, 266, 162 USPQ 170, 173 (CCPA 1969). Instead, whether an inventor's testimony is corroborated sufficiently should be evaluated using a "rule of reason." An evaluation of all pertinent evidence must be undertaken so that a sound determination of the credibility of an inventor's story can be made. *Price*, 988 F.2d at 1187, 26 USPQ2d at 1037. Circumstantial evidence of an independent nature may satisfy the corroboration requirement. *Cooper*, 154 F.3d at 1330, 47 USPQ2d at 1903. "In the final analysis, each corroboration case must be decided on its own facts with a view to deciding whether the evidence as a whole is persuasive." *Berges v. Gottstein*, 618 F.2d 771, 776, 205 USPQ 691, 695 (CCPA 1980).

C. The October 1991 activity

While Rose directed us to its pre-October 1991 activity in its principal brief, at oral hearing Rose indicated that it was not relying upon the activity as a conception and instead would be relying upon its October 1991 activity as an actual reduction to practice or at least a

conception of the invention of the count. (FFs 76 and 78).<sup>9</sup> Rose has not shown that the pre-October 1991 activity amounts to a conception at any rate. As noted by Dr. Sapp, possession of the necessary capsid protein encoding nucleic acid, baculovirus and Sf-9 cells in August of 1990 would have given Rose what was necessary to produce and test HPV VLPs with a *hope* that the VLPs would be conformationally correct. (FF 75). Without more, such a hope does not amount to the type of reasonable expectation that is necessary to establish a conception of an embodiment within the scope of the counts. *Hitzeman*, 243 F.3d at 1357, 58 USPQ2d at 1170.

Rose argues that it actually reduced to practice or at least conceived an embodiment falling within the scopes of the counts in October of 1991. At that time, Dr. Rose says that he observed binding between what he believed were VLPs and anti-sera from rabbits infected with HPV virions which would be indicative of VLPs having conformational epitopes. (FFs 80-83). Rose relies primarily upon the testimony of Dr. Rose which refers to portions of Dr. Rose's laboratory notebooks to prove the October 1991 activity. Rose argues that the October activity is substantially corroborated by:

- (1) the notebooks of Dr. Rose,
- (2) the testimony of the inventors,
- (3) the testimony of Dr. Rose's laboratory partner, Caroline Harvey,
- (4) the testimony of Dr. Garcea to whom Dr. Rose sent material for electron microscopic analysis,
- (5) the testimony of Marlene Shero, who prepared negatives from electron

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<sup>9</sup> At any rate, Rose could not prove a date of conception earlier than 25 July 1991 based on its statement in its preliminary statement that it did not disclose the invention to another until such date. (FF 77).

micrographs experiments involving samples sent to her by Dr. Rose in July and September of 1991, and

- (6) the testimony of Martha Smith, a laboratory technician in the Photography Unit at the University of Rochester (FF 84).

Even if we were to agree with Rose that the October 1991 activity, to which Dr. Rose testified, amounts to at least a conception of an invention within the scope of the counts, Rose has not provided independent corroboration of Dr. Rose's testimony that is required even under a rule of reason analysis. The problem with Dr. Rose's testimony regarding the October 1991 activity, in particular the RIPA testing and the results thereof, is that there is insufficient independent corroboration of the activity described by Dr. Rose in his testimony. Without the RIPA results, Rose could not have had even a conception since Rose could not have had a reasonable expectation of successfully producing HPV VLPs having conformationally correct epitopes.

1. The notebooks (FF 85)

The largest difficulty we have with Dr. Rose's notebooks is that it does not appear that the pages thereof have been witnessed. In particular, we do not see where a witness signed the notebook pages and we have not been directed to testimony from anyone who is said to have witnessed the pages. Moreover, Dr. Rose's notebooks appear to be of the "loose-leaf" type and thus capable of having pages easily added or subtracted. In general we are inclined to accord less weight to "loose-leaf" type notebooks than bound or otherwise secure notebooks that are not as easily modified after the fact. We find that the absence of witnessed pages (and witness testimony) combined with their loose-leaf character, severely limits the corroborative value of the

notebooks.

Accordingly, the notebooks do not provide adequate evidence independent of Dr. Rose that corroborates his testimony in this interference.

2. Coinventor testimony (FF 86)

Rose argues that the inventor testimony corroborates the October 1991 activity. Rose does not direct us to any particular testimony of the inventors other than Dr. Rose. At any rate, we do not consider the testimony of Dr. Bonnez and Dr. Reichman to be independent sources of corroboration since each is part of the inventive entity of Rose. *Manny v. Garlick*, 135 F.2d 757, 768, 57 USPQ 377, 388 (CCPA 1943). Even were it is appropriate for us to look to the testimony of Dr. Rose's coinventors to corroborate Dr. Rose's testimony, we have not been directed to testimony from either Dr. Bonnez or Dr. Reichman indicating that either of the inventors periodically reviewed Dr. Rose's work towards obtaining HPV VLPS and more to the point, that either was made aware, contemporaneously, of the RIPA test results said to have been obtained by Dr. Rose in October of 1991.

3. Ms. Harvey's testimony (FFs 87-89)

Ms. Harvey says she was generally aware that Dr. Rose was trying to produce HPV L1 protein in insect cells using the baculovirus system and to test the immunological properties of the produced L1 protein. Ms. Harvey's testimony does not corroborate Dr. Rose's testimony that he performed a RIPA in October of 1991 and obtained the results Dr. Rose is said to have obtained. Ms. Harvey's general awareness of Dr. Rose's efforts to test the immunological properties of recombinantly produced L1 from 1990 to 1992 is too vague to corroborate Dr. Rose's testimony regarding the allegedly successful RIPA said to have been analyzed in October

of 1991.

4. Dr. Garcea's testimony (FFs 90-95)

The portion of Dr. Garcea's testimony upon which Rose relies indicates that Dr. Rose may have sent a package containing (1) the complete L1 coding sequence of HPV-6b, (2) the complete L2 coding sequence of HPV-6b, and (3) a 735 bp HPV-11 E1-E4 cDNA to Dr. Garcea in October of 1991. On its face, the fact that samples were sent for electron micrograph testing for the presence of VLPs, does not confirm that Dr. Rose had obtained successful serological results, i.e., results indicating the presence of conformationally correct epitopes in his samples. Thus, we hold that Dr. Garcea's testimony does not corroborate sufficiently Dr. Rose's testimony regarding the RIPA results of October 1991.

5. Ms. Shero's testimony (FFs 96-99)

Ms. Shero's testimony is similar to Dr. Garcea's in that it relates to requests from the inventors to have Ms. Shero prepare electron micrographs of Sf-9 cells that were believed to have expressed VLPs. Ms. Shero testified that these requests occurred in July and September of 1991. As with Dr. Garcea's testimony, the fact that samples were sent to Ms. Shero does not, on its face, confirm that successful serological results, i.e., results indicating the presence of conformationally correct epitopes, had been obtained by Dr. Rose. Accordingly, we hold that Ms. Shero's testimony does not corroborate sufficiently Dr. Rose's testimony regarding the RIPA results of October 1991.

6. Ms. Smith's testimony (FFs 100-105)

Ms. Smith's testimony indicates that certain "orders" were brought to her or her husband for photographing at various time from September of 1990 through September of 1992.

Photocopies of the front of the envelopes, each labelled with a date and a serial number and which are said to have contained the orders, are found in Dr. Rose's laboratory notebooks.<sup>10</sup> Ms. Smith's testimony indicates that she or her husband labelled the envelope fronts and that the photographs taken were stamped on the back with the serial number. Copies of what appear to be these envelope fronts and what may be the backs of these photographs appear in Dr. Rose's notebooks. (See, e.g., Exh. 4128 at 25 and 24A). Ms. Smith's testimony combined with the portions of Dr. Rose's notebooks to which it directs us show only that an "order" was brought for photographing on a particular date and not what the "order" was. The copies of what may be the backs of photographs, particularly in the context of a loose-leaf notebook, do not shed any further light on what appeared on the front of the photograph.

Rose has not directed us to testimony from Ms. Smith indicating that she actually saw a particular test result that was photographed. Rose has not directed us to an envelope front that is said to correspond with the October 1991 RIPA results and Ms. Smith does not testify that she ever saw the RIPA results. We do not find it is necessary for Ms. Smith to have been able to understand the contents of the results photographed in order for her testimony to act as corroborative evidence. *Price*, 988 F.2d at 1194, 26 USPQ2d at 1037. However, in her declaration, (Exh. 4144), Ms. Smith does not testify that she ever saw the results of the RIPA in October of 1991 or any other results brought to her or her husband for photographing. Thus Ms.

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<sup>10</sup> While this was not pointed out to us by Rose in its principal briefs, it also appears that Dr. Rose's notebook contains some photocopies of what may be the backs of photographs stamped with the order numbers found on the envelopes. (See, e.g., Exh. 4128 at page 26A). These copies appear on separate pages from what is said to be the copies of the front of the photographs. We were not directed to any photograph having the order number printed on its front such that we could perhaps use the order number to surmise when the photograph was taken.

Smith's testimony is not sufficient to corroborate that the RIPA results, testified to by Dr. Rose, existed in October of 1991 nor is her testimony adequate to corroborate any other test result which she or her husband is said to have photographed.

7. The combined evidence

When we consider each individual piece of evidence pointed out to us by Rose in support of corroboration of Dr. Rose's testimony on the October 1991 activity, we determine that none of the evidence is sufficient individually for reasons noted above. However, we recognize that conception can be proven even though no one piece of evidence in and of itself establishes the prior conception. If the picture painted by all the evidence leads to "an abiding conviction" that prior conception is "highly probable", that is enough. *Price* 988 F.2d at 1196, 26 USPQ2d at 1038. Nonetheless, corroboration that is not dependent solely on the inventor is necessary for corroboration, even under a rule of reason analysis. *Reese*, 661 F.2d at 1224, 211 USPQ at 947. The independent circumstantial evidence Rose relies upon for corroboration does not confirm the substance and the date of the activities testified to by and reported in Dr. Rose's notebooks. In particular, the requirement for conformational correctness found in each count has not been established as of October 1991. While the independent corroborative evidence pointed out to us by Rose leads us to believe that Dr. Rose was attempting to produce HPV VLPs during the relevant time frame, we have not been directed to corroborative evidence independent of Dr. Rose that reasonably confirms that Dr. Rose obtained the RIPA results in October of 1991.

D. The 15 July 1992 activity

Schlegel has been accorded a priority benefit date of 25 June 1992. The activity of July 1992 occurs after the priority benefit date accorded to Schlegel and thus is insufficient to show

priority as to Schlegel.

Frazer has been accorded a priority benefit date of 20 July 1992. Lowy has been accorded a priority benefit date of 3 September 1992. Rose's activity of July 1992 occurs before the benefit date accorded to either Frazer or Lowy, and thus potentially could be relied on as part of a proof of priority as to Frazer or Lowy.

Rose argues that if the October 1991 activities were not enough to establish an actual reduction to practice of the invention, then the electron microscopy results received on 15 July 1992 were. (Paper 143 at 39). As discussed supra, Rose has not shown sufficient corroboration of the October 1991 activity. In particular, Dr. Rose's testimony and laboratory notebooks regarding the October 1991 RIPA results were not corroborated sufficiently.

Dr. Garcea's testimony (FFs 111 and 112) is consistent with that of Dr. Rose regarding the electron micrograph results of July 1992. However, we have not been directed to evidence sufficient to show that the electron micrograph results, without successful RIPA or equivalent serological testing results, would have led to a reasonable expectation that conformationally correct epitopes could be obtained such that a conception may have occurred. Dr. Garcea's testimony and Dr. Sapp's testimony indicate that immunological testing is necessary to show the presence of conformationally correct epitopes. (FFs 115-119). As discussed supra, each count requires conformational correctness. Based on the record before us and the complexity and uncertainty of the technology involved, we find that, until the VLPs Rose obtained were shown to show some signs of being conformationally correct, e.g., shown to react with antibodies to a native HPV virion, there could not have been a reasonable expectation that the inventors could produce an invention of the counts. Accordingly, we hold that Rose has failed to prove that it



had conceived an invention of the counts in July of 1992.

The priority benefit date accorded to Frazer is 20 July 1992. Since Rose has not shown a conception prior to 20 July 1992, Rose cannot prevail on priority as to Frazer.

E.     The August and September 1992 activity

Rose directs us to further activity in August and September of 1992 when Rose states that additional serological testing was undertaken focusing on immuno-dotblot assays using rabbit, mouse, and human sera. (FFs 120,121). Rose relies on the testimony and laboratory notebook pages of Dr. Rose to show the August and September 1992 activity which Rose says establishes a further actual reduction to practice. (Paper 143 at 51).

Rose directs us to exhibits from Dr. Rose's laboratory notebook which Rose says show the actual test results and the testimony of Ms. Smith as corroborative of Dr. Rose's testimony.

The Rose evidence is insufficient to establish the August/September activity as described by Dr. Rose. In particular, Rose has not directed us to evidence sufficient to corroborate Dr. Rose's testimony and unwitnessed laboratory notebooks as such relate to the August and September 1992 activity.

The notebook pages and Ms. Smith's testimony regarding the August and September 1992 activity suffer from the same deficiencies as the notebook pages and testimony regarding the October 1991 activity. While it does appear that test results may have been taken to the Photography Unit during the relevant time frame based on the envelope fronts (FFs 128-131), Ms. Smith does not identify a particular photograph such that we can conclude that the

photograph existed in August or September of 1992. (FF 132).<sup>11</sup> We have not been directed to testimony from Ms. Smith indicating that she remembers seeing a particular immunodot-blot result.

When we consider the corroborative evidence pointed out to us by Rose as a whole, we determine that Rose has not met its burden of showing independent corroboration of Dr. Rose's testimony and laboratory notebooks as to the August and September 1992 activity. While the corroborative evidence pointed out to us by Rose leads us to believe that Dr. Rose may have been attempting to produce HPV VLPs during the relevant time frame, we have not been directed to corroborative evidence that reasonably confirms that Dr. Rose obtained, in August or September of 1992, the serological results to which Dr. Rose testified.

Lowy was accorded a priority benefit date of 3 September 1992. Since Rose has not shown a conception prior to 3 September 1992, Rose cannot prevail against Lowy.

#### F. Diligence

To the extent we are incorrect in our determination and a reviewing court concludes that Rose has established a conception that was earlier than that of any of Schlegel, Rose, or Lowy, diligence would become an issue. At oral hearing Rose indicated that its diligence began in February 1992 (FF 135). Rose primarily relies upon the testimony and unwitnessed laboratory notebook pages of Dr. Rose to show diligence during the relevant time frame. (FF 136).

To corroborate Dr. Rose's testimony and notebook pages, Rose directs us to the

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<sup>11</sup> Each of the envelope fronts from Dr. Rose's notebook to which Ms. Smith refers in her testimony has the marking "2 Blot" in the left hand corner (see Exh. 4128 at 79 and 4129 at 132) but Ms. Smith has not testified that this would mean that an immunodot-blot result had been brought in for photographing or that she remembered seeing an immunodot-blot result on the relevant dates.

testimony of Dr. Garcea, Ms. Smith, and Ms. Harvey. The testimony of each has been discussed supra. While the portions of Dr. Garcea's testimony to which Rose directs us are sufficiently corroborative of the July activity (i.e., the visualization through electron microscopy) (FF 142-145), the other testimony to which Rose directs us is insufficient to corroborate the other activity upon which Rose relies for diligence. In particular, as discussed above, neither the testimony of Dr. Garcea, Ms. Smith, nor Ms. Harvey indicates sufficient awareness of Dr. Rose's activities as they relate to actually reducing to practice an invention of the Counts from February to mid-July and in August and early September of 1992.

G. Alternatives of the count

In each interference, Rose directs the majority of its efforts toward showing a conception and actual reduction to practice within the alternatives of the counts that are Rose's claims. However, in each interference, Rose makes an argument that it can also meet an alternative of the count that is defined by at least one of its opponent's claims that was held to be unpatentable to the opponent in the context of an interference to which Rose was not a party.

1. The '771 interference

As noted by Rose, in the '775 interference to which Rose is not a party and in which Rose has no standing, we determined that Lowy claim 48, an alternative of the count, reads on an isolated native HPV virion. (FF 23). On this basis, Rose asks that we accept its proofs to isolated HPV virions as evidence that it was prior to Lowy.

Rose has not directed us to evidence or argument that, on this '771 record, supports the interpretation of Lowy claim 48 that Rose urges. Indeed, all Rose has done here is point to a decision in the '775 interference which, based on the evidence and arguments presented in the

'775 interference, held that Lowy claim 48 reads on an isolated native HPV virion. (FF 23).

Each interference is decided on the record of that particular interference. Rose's failure to provide evidence or argument that, on this '771 record, support the Count interpretation Rose urges is adequate reason to reject Rose's priority proofs directed to isolated native HPV virions.

In any event and since it has been raised by Rose, it is worth noting that Lowy claim 48 has been held to be unpatentable over prior art<sup>12</sup> in the context of the '775 interference. In so holding the motions panel construed Lowy claim 48 to encompass isolated native HPV virions. Rose cannot prevail on priority to the extent its proofs are directed to isolated native virions since the subject matter is not patentable to Lowy and Rose has not tried to prove that the subject matter is patentable to Rose. The purpose of a count in an interference is to define the scope of evidence that may be offered to prove priority of the commonly claimed patentable invention. *See Perkins v. Kwon*, 886 F.2d 325, 327, 12 USPQ2d 1308, 1310 (Fed. Cir. 1989).<sup>13</sup> Thus, even if we were to accept Rose's construction of Lowy claim 48, we would reject Rose's proofs to isolated native virions.

To the extent that, upon review, the holding in the '775 interference that Lowy claim 48 is unpatentable is found to be in error, then it is likely that the proofs upon which Rose relies to show priority as to the Lowy claim 48 alternative of the count would no longer be relevant. In particular, if Lowy claim 48 is determined not to encompass isolated native HPV virions, then

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<sup>12</sup> US Patent 5,071,757 to Kreider et al., filed 6 October 1986.

<sup>13</sup> Consistent with this idea that the count should define subject matter that is at least patentable over the prior art, Bd.R. 208(c)(2) requires that a party moving to substitute or add a count must show that the count is patentable over the prior art. Hence, to the extent that a count includes several alternatives, some of which are patentable and some of which are not, priority proofs must be within the scope of the patentable alternatives.

Rose's proofs to the isolated native virions would not show either a conception or actual reduction to practice of the count.

2. The '772 interference

As noted by Rose, in the '776 interference to which Rose is not a party and in which Rose has no standing, we determined that Schlegel claims 1 and 64, alternatives of the count, read on an isolated native HPV virion. (FF 49). On this basis, Rose asks that we accept its proofs to isolated HPV virions as evidence that it was prior to Schlegel.

Rose has not directed us to evidence or argument that, on this '772 record, supports the interpretation of Schlegel claims 1 and 64 that Rose urges. Indeed, all Rose has done here is point to a decision in the '776 interference which, based on the evidence and arguments presented in the '776 interference, held that Schlegel claims 1 and 64 read on an isolated native HPV virion. (FF 49). Rose's failure to provide evidence or argument that, on this '772 record, support the Count interpretation Rose urges is adequate reason to reject Rose's priority proofs directed to isolated native HPV virions.

In any event and since it has been raised by Rose, it is worth noting that Schlegel claims 1 and 64 have been held to be unpatentable over prior art<sup>14</sup> in the context of the '776 interference. In so holding the motions panel construed Schlegel claims 1 and 64 to encompass isolated native HPV virions. For reasons stated above, Rose cannot prevail on priority to the extent its proofs are directed to isolated native virions since the subject matter is not patentable to Schlegel and Rose has not tried to prove that the subject matter is patentable to Rose. Thus, even if we were to accept Rose's construction of Schlegel claims 1 and 64, we would reject Rose's proofs to

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<sup>14</sup> US Patent 5,071,757 to Kreider et al., filed 6 October 1986.

isolated native virions.

To the extent that, upon review of our holding in the '776 interference that Schlegel claims 1 and 64 are unpatentable is found to be in error, then it is likely that the proofs upon which Rose relies to show priority as to Schlegel claims 1 and 64 alternatives of the count would no longer be relevant. In particular, if Schlegel claims 1 and 64 are determined not to encompass isolated native HPV virions, then Rose's proofs to the isolated native virions would not show either a conception or actual reduction to practice of the count.

### 3. The '773 interference

As noted by Rose, in the '775 interference, to which Rose is not a party and has no standing, we determined that Frazer claim 91, an alternative of the count, reads on an isolated native HPV virion. On this basis, Rose asks that we accept its proofs to isolated HPV virions as evidence that it was prior to Frazer.

Rose has not directed us to evidence or argument that, on this '773 record, supports the interpretation of Frazer claim 91 that Rose urges. Indeed, all Rose has done here is point to a decision in the '775 interferences which, based on the evidence and arguments presented in the '775 interference, held that Frazer claim 91 reads on an isolated native HPV virion. (FF 68). Rose's failure to provide evidence or argument that, on this '773 record, support the Count interpretation Rose urges is adequate reason to reject Rose's priority proofs directed to isolated native HPV virions.

In any event and since it has been raised by Rose, it is worth noting that Frazer claim 91 has been held to be unpatentable over prior art<sup>15</sup> in the context of the '775 interference. In so

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<sup>15</sup> US Patent 5,071,757 to Kreider et al., filed 6 October 1986.

holding the motions panel construed Frazer claim 91 to encompass isolated native HPV virions. For reasons stated above, Rose cannot prevail on priority to the extent its proofs are directed to isolated native virions since the subject matter is not patentable to Frazer and Rose has not tried to prove that the subject matter is patentable to Rose. Thus, even if we were to accept Rose's construction of Frazer claim 91, we would reject Rose's proofs to isolated native virions.

To the extent that upon review of our holding in the '775 interference that Frazer claim 91 are unpatentable is found to be in error, then it is likely that the proofs upon which Rose relies to show priority as to the Frazer claim 91 alternatives of the count would no longer be relevant. In particular, if Frazer claim 91 are determined not to encompass isolated native HPV virions, then Rose's proofs to the isolated native virions would not show either a conception or actual reduction to practice of the count.

#### H. Frazer motions to suppress

In its miscellaneous motions 19 through 24 ('773, Papers 232-237), Frazer moves to exclude certain Rose exhibits or portions of certain Rose exhibits and to strike portions of the Rose reply brief. Rose does not prevail even when we consider these exhibits and portions of exhibits that are relied upon in Rose's principal brief. Since Rose did not set forth a prima facie case establishing that it was prior to Rose, we have not considered the Rose reply and the exhibits relied upon therein. Accordingly, we do not find it necessary to decide Frazer miscellaneous motions 19 through 24 and therefore dismiss the motions.

#### IV. Conclusion

Since Rose has not established a conception date that is prior to the priority benefit dates accorded to its opponents, Rose cannot prevail. Rose did not establish a *prima facie* case for priority in its Briefs. Thus we have not considered its opponents' Oppositions or Rose's Replies thereto. Judgment adverse to Rose shall be entered as to each count.

Frazer miscellaneous motions 19 through 24 are DISMISSED as moot.

/ss/ Fred E. McKelvey	)	
FRED E. McKELVEY, Senior	)	
Administrative Patent Judge	)	
	)	
	)	
/ss/ Sally Gardner Lane	)	
SALLY GARDNER LANE	)	
Administrative Patent Judge	)	BOARD OF PATENT
	)	APPEALS AND
	)	INTERFERENCES
/ss/ Michael P. Tierney	)	
MICHAEL P. TIERNEY	)	
Administrative Patent Judge	)	
	)	
	)	
/ss/ James T. Moore	)	
JAMES T. MOORE	)	
Administrative Patent Judge	)	
	)	
	)	
/ss/ Mark Nagumo	)	
MARK NAGUMO	)	
Administrative Patent Judge	)	



Appendix: Technical Background  
for interferences 104,771 through 104,776

The following appendix is provided as an executive summary of the technical background underlying interferences 104,771 through 104,776. It is intended to be a convenient non-technical guide for those readers who are not familiar with the technology or the discussions in the Decisions on Preliminary Motions in the respective interferences. We have tried to keep it simple by not presenting the subtleties of the art or the points of disagreement. Those familiar with the art will recognize the oversimplifications. Moreover, we have not cited the record. Detailed findings of fact are set out throughout the decisions and opinions, which stand independently of this appendix. Although we believe this summary is accurate and consistent with the findings of fact and the conclusions drawn in the decisions and opinions, it is in no way a substitute for the detailed findings of fact.

Papillomaviruses

Papillomaviruses infect a wide variety of animals, typically giving rise to growths (warts) that may be painful or unsightly, but usually not malignant. The viruses are highly species and tissue specific. For example, the virus that gives rise to plantar warts on the soles of the feet of human beings (HPV-1) will not infect other human tissues, such as oral membranes, or any tissue of any non-human animal. By 1990, more than 50 distinct human papillomaviruses had been identified on the basis of differences among their DNA sequences, usually determined by DNA-matching ("hybridization") experiments.

Certain human papillomaviruses give rise to ano-genital warts, and certain of these

viruses have been established as causative agents of cervical cancer. The type 16 human papillomavirus ("HPV-16") was the first virus implicated as a causative agent of cervical cancer. HPV-16 was identified by extracting viral DNA from an advanced cervical tumor and comparing it to the DNA of other human papillomaviruses by hybridization experiments. Because it had a low degree of hybridization (*i.e.*, did not match) with other types, it was assigned a new type number, "16." Eventually, the DNA was sequenced, and samples were distributed to numerous laboratories around the world. This first isolated and sequenced HPV-16 DNA came to be called the "prototype HPV-16" DNA. The DNA of other HPV-16s and other papillomaviruses were also isolated and used in artificial genes to make virus proteins. Several other HPV types have also been implicated as giving rise to cervical cancer.

Papillomaviruses have a protein coat or shell made of two proteins, called "L1" and "L2." The L1 protein forms the outermost shell of the papillomavirus. The exact location of the L2 protein is not known, but it is thought to be in the interior of the shell.

### Virus-like particles

When viruses infect cells, the viruses take over the cellular machinery and reproduce the viral DNA and all the proteins that make up the virus. The viral coat proteins often pack spontaneously around the viral DNA to form the mature viruses. Even in the absence of the viral DNA, the viral coat proteins may aggregate to form particles having the approximate size and shape of the native virus. Such particles, if they do not contain the viral DNA, are generally referred to as "virus-like particles."

We have not been directed to any evidence of reports of recombinantly-produced virus-like particles from papillomaviruses prior to the work at issue in these interferences.

### Vaccines

The immune system can protect the body against invading viruses via antibodies to the outermost coat of the virus. Any given type of antibody will bind only to a specific site having a particular molecular shape or "conformation." Antibodies that bind to specific sites, called "epitopes," on the surface of an intact virus, are said to bind to "conformational epitopes." If the antibodies bind to all the receptor sites on the virus that the virus uses to bind to cells, receptor sites will be blocked, and the ability of the virus to infect cells will be neutralized.

Antibodies are made by specialized cells. A given antibody-making cell makes antibodies that recognize only one specific epitope. When the individual is exposed to a particular virus, the cells that make the antibodies that recognize the protein coat of that virus will be stimulated to make more antibodies, and they will remember that virus. Upon future exposure to that virus, the individual's immune system will be prepared to make large quantities of those antibodies.

Vaccines work by priming the immune system to produce large numbers of neutralizing antibodies to particular viruses. In some cases, the patient can be exposed to a killed or weakened strain of the virus rather than the active virus itself. The process of killing or weakening the virus, however, may change the exposed surface of the virus so much that few antibodies to the active virus are activated. It is also possible that the killed or weakened virus may be re-activated, leading to infection and disease rather than immunization.

A gene is a DNA molecule that carries the genetic code that instructs the cell how to make a particular protein. Genetic engineering using so-called "recombinant" techniques involves "recombining" a foreign gene with the genes of a host cell. Then the machinery of the host cell is harnessed to make the protein coded for by the foreign gene. That protein can be made in large quantities, isolated, and purified. These recombinant techniques brought hopes that the coat proteins of viruses could be produced in large quantities, cheaply, easily, and completely free of viral DNA.

If the recombinant viral coat protein had the same conformational epitopes as the proteins in the native virus, it might serve as a vaccine. Because the protein would not be subjected to the process of weakening or killing the virus, it might be more effective at priming the immune system to make antibodies against the virus than vaccines made from viruses. Moreover, a vaccine made from such proteins would carry no risk of inducing the viral disease, such as cervical cancer. Given the tendency of many viral coat proteins to form virus-like particles, the virus-like particles, if they had the conformational epitopes of the native virus, could also serve as vaccines.

Only a couple of reports of vaccines based on recombinantly produced virus-like particles appear in the record as "prior art" to the applications involved in these interferences. The most prominent example in the record of a prior-art recombinant viral coat protein vaccine is that for hepatitis-B, which was the subject of the interference reported in *Hitzeman v. Rutter*, 243 F.3d 1345, 58 USPQ2d 1161 (Fed. Cir. 2001).

### Diagnostic reagents

In addition to uses as vaccines, recombinantly produced viral coat proteins having the conformational epitopes of the L1 protein of the native virus could also be used as diagnostic reagents to determine whether an individual had been exposed to a particular type of papillomavirus. Serum from the individual would be checked for the presence of antibodies to the papillomavirus by looking for reaction with the recombinant protein. A significant degree of reaction between the recombinant protein and the serum would indicate that the serum contained an elevated level of antibodies to the papillomavirus, indicating exposure of the patient to that virus.

### Proofs of the parties

In their proofs for conception and actual reduction to practice, the parties have attempted to show why their laboratory work at various stages provided sufficient evidence that various limitations of the Counts, particularly the existence of conformational epitopes, had been demonstrated. The parties mutually have challenged the sufficiency of proof each has offered for conception and actual reduction to practice of the counts in the various interferences. In briefest outline, the positions of the parties follow.

Frazer discloses, in its Australian, PCT, and involved applications, particles made from the L1 and L2 proteins of an HPV-16 virus. These particles are significantly smaller (average diameter reported to be 35–40 nm) than all known papillomaviruses (diameters reported to be 50–60 nm). These particles are also irregularly shaped, rather than essentially spherical or icosahedral. Frazer presents no credible evidence that indicates that these particles have

conformational epitopes of the native HPV-16 virus. Instead, Frazer maintains that such conformational epitopes are inherently present in the particles it produced. Frazer's position has not been accepted, and it has been denied the benefit for priority of its Australian application. (In contrast, the particles from other papillomaviruses disclosed in Frazer's PCT application and in its involved application are about 50 nm in diameter and regularly shaped. Motions by Frazer's opponents that the disclosures of these particles failed as constructive reductions to practice of the Count were unsuccessful in the preliminary motions phase. Thus, Frazer was accorded the benefit for priority of its PCT application.)

Schlegel discloses L1 protein from HPV-1, together with experimental evidence that it maintains shows that the L1 protein has the conformational epitopes of the L1 protein in the native virion. Schlegel reports, however, that it looked for but did not find evidence indicating the presence of virus-like particles in its L1 protein preparations.

Lowy discloses virus-like particles and experimental evidence that it maintains shows that the virus-like particles it reports have at least one conformational epitope of the native virus and are capable of inducing neutralizing antibodies to the native virus.

Rose discloses virus-like particles and experimental evidence that it maintains shows that the virus-like particles it reports are conformationally correct and are recognized by antibodies from patients, including human patients, infected by the corresponding virus.

More detailed summaries of the technology and of particular technical issues involved in individual interferences may be found in the various decisions on preliminary motions and decisions on priority dates. We emphasize again that this summary is not a substitute for formal findings of fact in the decisions on priority dates.

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